

Nomograms for Predicting Annual Resolution Rate of Primary Vesicoureteral Reflux: Results From 2,462 Children

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Purpose: We determined the resolution rate of vesicoureteral reflux and the factors that influence it to formulate nomograms to predict the probability of annual resolution for individual cases of reflux.

Materials and Methods: We studied 2,462 children with primary vesicoureteral reflux diagnosed between 1998 and 2006. Cox proportional hazards regression was used to model time to resolution as a function of statistically significant demographic and clinical variables. The resulting model was used to construct nomograms predicting the annual cumulative probability of reflux resolution.

Results: Multivariate analysis showed that all cases of unilateral reflux resolved earlier than female bilateral reflux (HR 1.42, $p < 0.001$). Additionally age less than 1 year at presentation (HR 1.31, $p < 0.001$), lower reflux grade (2.96, $p < 0.001$ for grade I; 2.28, $p < 0.001$ for grade II; 1.63, $p < 0.001$ for grade III), reflux diagnosed on postnatal evaluation for prenatal hydronephrosis or sibling screening (1.24, $p = 0.002$) and single ureter (1.55, $p < 0.001$) were associated with significantly earlier resolution of reflux. Specific predicted cumulative probabilities of reflux resolution at annual intervals from diagnosis (1 to 5 years) were calculated for every possible combination of the significant variables.

Conclusions: Our analyses demonstrate that resolution of vesicoureteral reflux is dependent on age at presentation, gender, grade, laterality, mode of clinical presentation and ureteral anatomy. We constructed nomogram tables containing estimates of annual reflux resolution rate as a function of these variables. This information is valuable for clinical counseling and management decisions.

Key Words: nomograms, treatment outcome, vesico-ureteral reflux

MANAGEMENT of vesicoureteral reflux is challenging, and the debate regarding its clinical significance underpins the lack of consensus on whom, when and how to treat.¹ Reflux is routinely managed by prophylactic antibiotics and watchful waiting, although the efficacy of antibiotics has recently been challenged in randomized controlled trials.^{1,2} Following diagnosis repeat

radiological assessments of reflux are performed at an interval of 1 to several years between studies.^{3,4} This approach is based on the assumption that most cases resolve spontaneously with time.⁵⁻⁷

Three studies from 1987 to 1992 were used to formulate the 1997 Pediatric Vesicoureteral Reflux Guidelines.^{4,6,8,9} While these guidelines have

Abbreviations and Acronyms

PNH = prenatal hydronephrosis

RNC = radionuclide cystogram

UDS = urodynamics

US = ultrasound

UTI = urinary tract infection

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

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served as a general reference for predicting the resolution of VUR, they are based on relatively small clinical series. Several other studies published recently describe the natural history of reflux and provide data to aid in predicting spontaneous resolution.^{5,10–12} The ability to predict resolution of VUR has become increasingly important due to 1) the availability of a Food and Drug Administration approved, minimally invasive endoscopic treatment option for reflux, which may influence the timing of surgical intervention because of its purported simplicity and efficacy; 2) the potential but as yet unproved long-term risks associated with use of prophylactic antibiotics, including resistant infections and cancer; and 3) the possibility that prophylactic antibiotics are ineffective.^{1,2,13–16}

We sought to define more completely the factors that influence the resolution of VUR, and provide a means to predict reliably the spontaneous resolution of VUR based on clinical variables that are universally and reliably attainable. This information will aid practitioners and families with clinical management decisions.

MATERIALS AND METHODS

Institutional review board approval was obtained for the study. Patient records were de-identified before data extraction.

Patient Database and Evaluation

An electronic longitudinal database of all VUR cases has been maintained at our institution since 1998. All referred cases are entered into the database, and all initial and followup data are maintained and managed by a dedicated clinical research staff member. Inclusion criteria for the study were primary VUR and at least 1 followup visit with a cystogram. Primary VUR was differentiated from secondary VUR by exclusion of patients with anatomical or functional obstructive processes, eg posterior urethral valves and spina bifida, that could cause VUR. We did not exclude patients receiving anticholinergic medications, since these data were not readily available.

All patients underwent initial radiological assessment with VCUG, and renal and bladder US. VUR grade (I to V) was assigned according to the International Reflux Study in Children. Annual followup studies included either VCUG or RNC and US.

Complete ureteral duplication was defined as evidence of such on VCUG and US. The radiology department provided all radiological interpretations, which were confirmed by review of hospital electronic records before analysis of extracted data. If a discrepancy was noted between data in the database and hospital records, the study was reassessed by a urologist and a consensus was reached among investigators. In patients with bilateral VUR the recorded grade reflected the more severe side. Patients with changes in laterality, ie initial presentation of unilateral VUR and subsequent discovery of bilateral or initial bilateral and subsequent unilateral VUR, were clas-

sified as having bilateral VUR. The primary end point was spontaneous resolution, which was defined as 1 negative VCUG or RNC. All data were recorded from the annual visits until resolution of VUR or surgical intervention, and from patients still being followed or those with no further followup after 2 consecutive VUR studies.

Statistical Analysis

Baseline patient and clinical characteristics were summarized with counts and percentages for categorical variables, and means and standard deviations for continuous variables. Univariate Cox proportional hazards models were used to estimate the association between time to VUR resolution and each of the demographic and clinical variables. Times to resolution for subjects who underwent surgery were censored at the last visit preoperatively. Similarly for subjects who were still being followed or had no further followup time to resolution was censored at the last visit. The assumption of proportional hazards was confirmed graphically. Parametric survival models were used to evaluate the impact of the interval censoring resulting from the yearlong intervals between followup visits. The parametric model estimates did not differ materially from the proportional hazards model estimates. In the proportional hazards models tied events were handled using previously described methods.¹⁷

Univariate and multivariate analyses were conducted with the variables male vs female gender, age at presentation (younger than 1 year vs 1 year old or older), unilateral vs bilateral VUR, VUR grade (I to V), ureteral anatomy (single vs duplicated) and mode of presentation (PNH vs febrile UTI vs sibling VUR). Patients with nonfebrile UTI were excluded from these analyses, since we do not evaluate these patients for VUR. Univariate proportional hazards analyses revealed that VUR grades IV and V could be collapsed together, and that presentation could be grouped as PNH or sibling VUR vs UTI. Results of exploratory regression tree analyses showed that dichotomization of age at 0.83 years yielded the categorization of age with the optimal prediction of time to resolution. Therefore, age at presentation was dichotomized into younger than 1 year vs 1 year old or older in the proportional hazards models. We initially assigned arbitrary age groupings of less than 1 year (infancy), 1 to 4 years (not toilet trained) and older than 4 years (toilet trained) but these were not statistically valid. Other groupings, including cases divided into quartiles and each year examined individually, also failed to demonstrate significance.

We used multivariate Cox proportional hazards models to identify independent risk factors for faster time to VUR resolution. Variables were retained if their multivariate *p* value remained less than 0.05. Sensitivity analysis of the final model indicated that the parameter estimates were not affected by informative censoring in the group undergoing surgery. In other words, the model was tested to determine whether inclusion of the surgical group affected the nomogram values, and its inclusion did not have a significant effect. The resulting model was used to construct nomograms for the cumulative rate of VUR resolution through time for each possible combination of patient and clinical characteristics. Statistical analyses were performed using SAS® software, version 9.1.

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